REMARKS

Claims 13-23 are pending. No new matter has been added by way of the above amendments. For instance, the recitation of "bounded substance" has been removed from claims 13 and 14. Claims 13 and 14 have also been amended to recite that the substance "binds" rather being "able to bind." The preamble of claim 14 has also been clarified. Claim 19 has been amended to remove the recitation of "inter alia". Lastly, claim 21 has been amended to recite more clear grammar and to correct a minor typographical error. These amendments are non-narrowing in nature and do not constitute the addition of new matter.

In view of the following remarks applicants respectfully request that the Examiner withdraw all rejections and allow currently pending claims.

Objection to the Title

The Examiner has objected to the title of the invention. Accordingly, Applicants have submitted a new title for the Examiner's consideration. Accordingly, this objection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Issues under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 13-23 under 35 U.S.C. § 112, second paragraph, for the reasons recited at pages 5 and 6 of the outstanding Office Action. Applicants respectfully traverse these rejections.

First, the Examiner asserts that in claim 13, lines 5-6, the recitation of "is able to bind" should be replaced with "binds". Applicants have adopted this suggestion in the present claims. Thus, this rejection is moot.

Second, the Examiner asserts that the recitation in claim 13, line 7 of "bounded substance" is not understood. Applicants submit that the measurement being made is of the amount of substance bound to collagenase 3 mRNA or the amount of substance bound to collagenase 3. In such a measurement, it may be any portion of the substance, or collagenase 3 mRNA or collagenase 3, which is being measured. However, since in either case it is generically the bound collagenase 3 mRNA or the bound collagenase 3, which is being measured, Applicants have deleted the term "bounded substance" from the claims. This is a non-narrowing amendment. Accordingly, this rejection is moot.

Third, in the preamble of claim 14, the Examiner questions "what the predisposition is increased by is not seen"? Applicants traverse and submit that the preamble of claim 14 has been amended

to recite "detecting a genetic predisposition". Accordingly, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Fourth, the Examiner asserts that in claim 18, line 2, the recitation of "its" is unclear. Applicants traverse and submit that this claim term has been deleted. Thus, this rejection is moot.

Fifth, in claim 19, the Examiner asserts that the recitation of "inter alia operative interventions" lacks antecedent basis and is indefinite. Applicants traverse and submit that the phrase "inter alia" has been removed from the claim. Thus, this rejection is moot.

Sixth and lastly, the Examiner asserts that claim 21 is not understood concerning what markers are encompassed or how they are used. Applicants traverse and submit that the recitation of "wherein collagenase 3 and markers... are used" has been replaced with "wherein collagenase 3 is used as a marker". Thus, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

In view of the above, Applicants respectfully submit that the present claims are fully definite within the requirements of 35 U.S.C. § 112, second paragraph. Accordingly, the Examiner is

respectfully requested to withdraw all rejections and allow the currently pending claims.

Issues under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 13-23 under 35 U.S.C. § 112, first paragraph for the reasons recited of pages 2-3 of outstanding Office Action. In particular, the Examiner asserts that the present specification does not enable of skill in the art to make and/or use the invention. Applicants respectfully traverse this rejection.

First, the Examiner asserts that the data in Table 1 at page 8 of the present specification appears to be directed at the determination of whether there is a difference between "those who do and those who do not" show some unknown amount of collagenase 3 in the synovial membrane.

Applicants submit that Table 1 illustrates clinical and para-clinical data of 36 patients with rheumatoid arthritis, who represent one single cohort. Collagenase 3 mRNA was detected in synovial membrane specimens of 21 of these 36 patients (58%). In both subgroups, with and without collagenase 3 mRNA expression, the percentage of patients who were rheumatoid factor positive were determined. In the subgroup of patients with collagenase 3 expression, 14 of 21 patients (66%) had a positive rheumatoid

factor, and in the subgroup of patients without collagenase 3 expression, 9 of 15 patients (60%) were rheumatoid factor positive. Therefore, the percentage of patients who had a rheumatoid factor was similar in both subgroups. The rheumatoid factor is an unspecific autoantibody reflecting the degree of alterations in the immune system in may autoimmune diseases. The occurrence of the rheumatoid factor in the blood correlates predominantly with the duration of an autoimmune disease. The observation that the percentage of patients who had a rheumatoid factor was similar in both subgroups suggests an independent value of collagenase 3 for predicting the clinical course of rheumatoid arthritis, particularly with respect to the progression of cartilage and bone degradation. Accordingly, the data in Table 1 is fully clear to one of ordinary skill in the art.

Second, the Examiner asserts that there is no description of how the claimed method steps accomplish the functions as claimed and how one would use the data obtained from the method steps to accomplish any useful interpretation. Applicants respectfully disagree with the Examiner. As discussed above, very useful data is presented in the application. Also, Applicants submit that it is unexpected that the expression of a single MMP, collagenase 3, in the synovium would correlate with a clinical severe course of rheumatoid arthritis. As shown in the invention, other MMPs, like

interstitial collagenase (collagenase 1) and stromelysin 1, are in parallel expressed with collagenase 3 in rheumatoid arthritis (Fig.1). But, interstitial collagenase (collagenase 1) and stromelysin 1 are expressed in all patients and collagenase 3 is expressed only 58% of the cases. Furthermore, it was shown for interstitial collagenase and stromelysin 1, that their expression levels do not correlate with clinical severe courses of the disease. Accordingly, the present specification fully enables one of ordinary skill in the art to make and use the claimed invention.

In summary, Applicants respectfully submit that one of ordinary skill in the art would be fully able to make and/or use the invention as currently claimed, based upon the present specification. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Issues under 35 U.S.C. § 102(e)

The Examiner has rejected claims 13-23 under 35 U.S.C. § 102(e) as being anticipated by Falduto (USP 6,399,371) (hereinafter referred to as Falduto '371). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the disclosure of Falduto '371 fails to suggest or disclose determining collagenase 3 and rheumatoid arthritis. Instead, Falduto '371 relates to

polynucleotide sequences encoding matrix metalloprotease proteins (MMP), as well as methods which utilize these sequences, which are useful for the detection, diagnosis, staging, monitoring, prognosis, prevention, or treatment of cancer or inflammatory diseases. Falduto '371 discloses a MMP, provisionally named MMP-ABT, polynucleotide fragments thereof, expression vector containing those polynucleotides, host cells transformed with those expression vectors processes for making the MMP-ABT protein using those polynucleotides and vectors, isolated and purified MMP-ABT protein and fragments thereof, and antibodies raised to synthetic peptides derived from the MMP-ABT protein. Falduto '371 also discloses diagnostic assays to identify the MMP-ABT polynucleotide or polypeptide and the use as therapeutic agents of the MMP-ABT polynucleotide, polypeptides, or antibodies.

In Falduto '371, polynucleotide sequences of a putative and provisionally named MMP-ABT were obtained by screening a human cDNA expression database with consensus sequences to twelve other, already known human MMPs, among them collagenase 3. The techniques to obtain the provisionally named MMP-ABT and the methods for assaying the products of the MMP-ABT gene are all well known in the art. Although Falduto '371 suggest that such a MMP-ABT will aid in the diagnosis, staging, monitoring, prognosis and/or therapy of cancer and inflammatory diseases, no information is given in the

invention of Falduto '371 relative to collagenase 3 as a prognostic marker for rheumatoid arthritis.

In the section "Description of the related art" in column 2, lines 38 to end of Falduto '371, it is stated that an excess of MMPs activities is responsible for joint degradation in rheumatoid arthritis and osteoarthritis and the inhibition of this exacerbated degradative activities of MMPs by specific agents could help restore this balance. Indeed, experimental data suggest an imbalance between interstitial collagenase (collagenase 1) and stromelysin 1 and their major natural inhibitors TIMP1 and TIMP2 (see McCachren S.S. Arthritis Rheum. 34:1085-1092, 1991; Hembry R.M. et al., Ann. Rheum. Dis. 54:25-32, 1995). These data were obtained only for interstitial collagenase (collagenase 1) and stromelysin 1, and their natural inhibitors TIMP1 and TIMP2 at the levels of mRNA and protein expression. No data are available about the levels of activity of interstitial collagenase (collagenase 1), stromelysin 1, and other MMPs in the synovial membrane. Accordingly, the activity of collagenase 3 was also not determined in the synovial membrane. In addition, the major natural inhibitors of collagenase 3 are not known.

Furthermore, as shown in the disclosure Wernicke et al. (of record), interstitial collagenase (collagenase 1) and stromelysin 1 mRNA are expressed in all patients with rheumatoid arthritis,

whereas collagenase 3 mRNA was detected only in 58% of the cases (Figure 1). This observation illustrates that the expression of each particular MMP is very tightly regulated in a tissue and disease specific manner. It was shown for collagenase 3 that the gene of the MMP contains unique regulatory elements, which are very different from those of others MMPs, in particular of interstitial collagenase and stromelysin 1 (Pendás A.M. et al., Genomics 40: 222-233, 1997; Tardif G. et al., Biochem. J. 3223:13-16, 1997). The fact, that the expression of at least three MMPs (interstitial collagenase, stromelysin 1, and collagenase 3) in the synovial membrane in rheumatoid arthritis can be detected at the same time, is rather unusual. Therefore, although interstitial collagenase, stromelysin 1, and collagenase 3 are all members of the MMP gene family, it cannot be directly extrapolated to collagenase 3 from data obtained for interstitial collagenase (collagenase 1) and stromelysin 1.

In column 3, lines 36 to end of Falduto '371, a general statement is given about specific methods and reagents for the diagnosis, staging, prognosis, monitoring, prevention or treatment of diseases and conditions associated with imbalances in the production or activity of MMPs. These intentions as well as the methods to detect the production or activity of MMPs are all well known in the art. The major feature of MMPs, to be tightly

regulated in a tissue and disease specific manner and the unique regulation of the collagenase 3 gene, were already stressed (see above). Furthermore, the disclosure by Wernicke et al. was made to use collagenase 3 as a prognostic marker for the clinical course of rheumatoid arthritis and not as a target to block its catalytic activity in order to reduce the degradative activity in the synovial membrane.

Although Falduto '371 may contain general statements concerning using the disclosed MMP-ABT in diagnosing, staging, monitoring, prognosis and/or therapy of cancer and inflammatory diseases, Falduto '371 provides absolutely no information of the use of collagenase 3 as a prognostic marker for rheumatoid arthritis. Applicants remind the Examiner that there can be no anticipation where one skilled in the art would have to choose judiciously from a genus of possible combinations, In re Sivaramakrishnan, 213 USPQ 441, 673 F.2d 1382 (CCPA 1982), or where the reference does not highlight the claimed mixture, among the many dozens disclosed, or suggest the claimed ratio, In re Kollman et al., 201 USPQ 193, 595 F.2d 48 (CCPA 1979). At most the Examiner's rejection amounts to an "obvious to try" standard. "Obvious to try" is not a valid test of patentability. In re Mercier, 185 USPQ 774 (CCPA 1975); see also Hybritech Inc. v. Monoclonal Antibodies, 231 USPQ 81 (Fed. Cir. 1986).

In summary, the presently claimed subject matter is not anticipated by Falduto '371. Reconsideration and withdrawal of this rejection are respectfully requested.

In view of the above, Applicants respectfully submit that the present claims define subject matter, which is patentable over the cited art. Accordingly, the Examiner is respectfully requested to withdraw all rejections and allow the currently pending claims.

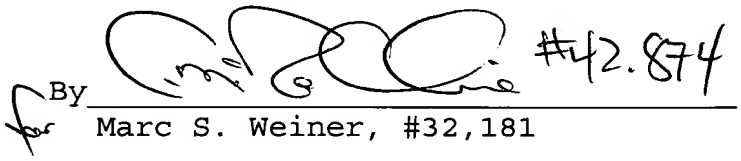
Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Craig A. McRobbie (Reg. No. 42,874) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. 1.17 and 1.136(a), the Applicants respectfully petition for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $55.00 is attached.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP



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